REMARKS

In the Office Action dated July 18, 2008, the Examiner: (1) withdrew the rejection of claims under 35 U.S.C. § 102(a or e); and (2) rejected claims 1, 38-54, 57-66, 68 and 70-91 under 35 U.S.C. § 103(a) as being unpatentable over Tuschl, *et al.*, Elbashir *et al.* and Walton *et al.* Although the Office Action Summary indicates that claims 44-51 and 70-77 are objected to, the undersigned attorney of record spoke with the Examiner, who clarified that the listing of those claims as "objected to" was an error. Accordingly, all pending claims were rejected as being obvious over the recited art. Applicants respond as follows:

The Examiner rejected the claims as obvious based on the premise that because the only concrete and tangible step of the instant claims is the synthesis of an siRNA molecule or a sequence having certain sequence requirements. She concluded: "siRNAs meeting these requirements are presumed to have been derived from the claimed method steps." (Office Action, p.3) Applicants respectfully submit that for at least eight reasons, the Examiner misapplied the standards for obviousness.

First, the "concrete and tangible" inquiry is applied when determining whether a claimed invention constitutes patentable subject matter under 35 U.S.C. § 101. See *e.g.*, *In re Nuijten,* 500 F.3d 1346, 1357 n.7 (Fed. Cir. 2007). It is not an inquiry that has a bearing on determining whether an invention is patentable under 35 U.S.C. § 103 or whether certain limitations carry more weight than others. After a claim is determined to be directed to patentable subject matter, there is no basis on which to distinguish which steps are or are not directed to concrete and/or tangible steps. As the Court of Appeals for the Federal Circuit illustrated in *AT&T v Corp. v. Excel Communications*, 172 F.3d 1352 (Fed. Cir. 1998), *cert. denied,* 528 U.S. 946 (1999) after considering whether a claimed invention (in that case a mathematical algorithm) produced a concrete and tangible result, the court advised that a separate inquiry would be needed under 35 U.S.C. §§ 102, 103 and 112. *Id.* at 1361. Accordingly, Applicants submit that the Examiner was not permitted to presume that Tuschl's recited sequences were derived by the claimed methods steps.

In order for the prior art to be deemed to have rendered the claimed methods obvious, each and every one of the recited method steps must have been taught by the prior art. In the absence of such a showing by the Examiner, the rejection is improper.

Second, the Examiner acknowledged that Tuschl failed to formalize his selection criteria. Applicants submit that Tuschl did not formalize selection criteria because he had no appreciation of the value of selection criteria such as Applicants' criteria, and a person of ordinary skill in the art upon reading Tuschl also would have no appreciation of their value.

Third, although the Examiner presumes that Tuschl selected his sequences based on Applicants' criteria, Tuschl itself describes how he chose his siRNA, and it is clear that he did not use Applicants' criteria or any selection criteria. In the examples of Tuschl, he started with a long dsRNA and observed the cleavage of this dsRNA into smaller siRNA before selecting the siRNA with which to work. See *e.g.,* Example 1.1.2; example 2.1.1; example 3.1.1. This empirical testing selection methodology was used to arrive at the sequences in Tuschl to which the Examiner points.

Fourth, Tuschl describes what he thought were the important criteria: length of dsRNA (1.2.1); variation in overhangs (3.2.1); and sequence effects due to nucleotide substitutions (3.2.5). He did not suggest looking to any of Applicants' criteria. Indeed, by referring to only those unrelated variables, the reference teaches away from Applicants' invention, and is further proof of the non-obviousness of Applicants' invention.

Fifth, the Examiner asserted "it is evident that Tuschl applied selection criteria that overlaps significantly such that siRNAs selected by Tuschl would necessarily also have been selected by the instant algorithm. Accordingly, since Tuschl *et al.* essentially teach the selection steps of the instant criteria as set forth in the algorithm, albeit for different reasons, the criteria of the algorithm are not novel." However, based on the foregoing, it is unclear as to how this is evident. Tuschl employed no selection steps that resemble Applicants' claimed methodology.

Applicants note that the Examiner has only shown that the prior art has taught to do step (b) of Applicants' claimed methodology – identifying the candidate siRNAs, she has not shown where the additional step of applying the criteria of the computer

algorithm with the recited criteria has been applied to the candidate siRNA (step (c) of the independent claims). Absent a teaching in the prior art to apply the criterion or criteria, the rejection is improper.

Sixth, the Examiner concluded that the only difference between Tuschl and the instant application is the use of the computer to run the selection criteria. As noted above, Applicants submit that this is incorrect, because Tuschl does not apply selection criteria that in any way suggest the ones specified by Applicants. Moreover, because Tuschl generated his siRNA based on empirical testing that would need to be done for each dsRNA that is processed into siRNAs, there would be no benefit to using a computer program. There would be nothing to automate, because in Tuschl's world there were no preferable features that were consistent across siRNA that target different genes.

Seventh, the Examiner cited Elbashir as teaching rules for designing siRNA molecules and that a more comprehensive list of evaluation of parameters to be considered for siRNA remains to be performed. Elbashir does not describe what that list might entail, nor does he suggest that one should consider the relative AU vs GC content within subregions of an siRNA, or suggest that one should consider non-target sequence specific base preferences. Additionally, he notes that as of 2002, "Selection of the targeted region is currently a trial-and-error process." (page 201) He proposes designing siRNAs with certain overhang content and notes that his rules merely provide a starting point for further experimentation. (201 –202) Thus, his teaching also supports a conclusion of non-obviousness and that in 2002 there was a need to find a better way to select siRNA and that one would need experimentation to determine what the selection parameters should be.

Eighth, the Examiner cited Walton for the proposition that it was known to use a prediction algorithm to identify antisense sequences with the highest predicted mRNA target-binding affinity. However, target-binding affinity is not the criteria on which Applicants' siRNA rationale design criteria are based. Instead, they rest on thermodynamic principles and ability to be processed by enzymes. Thus, were one to try to use mRNA target binding preferences, one would be led down the wrong path.

Applicants submit that no fee is necessary with this response. However, if any fee is deemed necessary, Applicants authorize the Patent Office to charge the Deposit Account No. 11-0171 for any such sum.

Respectfully submitted,

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